Electrophilic and Nucleophilic Reactivities of the Azomethine Carbon of SAMP-Hydrazones: Stereoselective Synthesis of γ-Amino Ketone Derivatives

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A novel methodology for the asymmetric synthesis of secondary *N*-Boc-protected γ-amino ketones is described. After the highly diastereoselective nucleophilic 1,4-addition of formaldehyde SAMP-hydrazone **1** to prochiral conjugated enones **2**, the carbonyl group of the resulting 4-oxo aldehyde SAMP-hydrazones **4** was protected as ethylene ketals **5**. The stereoselective (de 58−88%) addition of organometallic reagents to the CN double bond of the latter was then performed, and the unstable intermediate hydrazines obtained were either trapped as Moc-protected hydrazines **8** in good yields (65−87%) or reduced by Raney nickel-catalyzed hydrogenolysis of the N−N bond to afford the corresponding amines, which were isolated as their corresponding *N*-Boc derivatives **11**. Noteworthy, the azomethine carbon of SAMP-hydrazones, not being essentially modified during the process, sequentially serves as a nucleophilic and an electrophilic center, acting as a nexus between the conjugated enone (electrophile) and the organometallic reagent (nucleophile) and helping in the creation of two adjacent stereogenic centers.

Introduction

The nucleophilic character of the azomethine carbon of aldehyde *N*,*N*-dialkyl hydrazones was first studied in pioneering work by Brehme[1] and more recently by Kamitori,[2] who illustrated the aza-enamine behavior of these compounds by their reaction with several strong electrophilic reagents. On the basis of these investigations, we have demonstrated that the enhanced nucleophilicity exhibited by *formaldehyde N*,*N*-dialkyl hydrazones allows reactions with a broader palette of electrophilic substrates, including nitroalkenes,[3] α-alkoxy aldehydes,[4] conjugated enones,[5] and trifluoromethyl ketones.[6] If one combines these addition reactions with the efficient methods available for the transformation of the hydrazone moiety into formyl[7] or cyano[8] groups, these formaldehyde *N*,*N*-dialkyl hydrazones appear as a new class of neutral formyl anion and cyanide equivalents. Considering the lack of protocols available to perform asymmetric formylation reactions, particular efforts were directed to the development of chiral reagents to perform these reactions in an asymmetric way. One of the most important findings in this topic was the highly diastereoselective trialkylsilyl triflate-catalyzed Michael addition of formaldehyde SAMP-hydrazone **1**[9] to conjugated enones **2**.[5] Depending on quenching conditions, the 1,4-adducts exclusively formed in this reaction could be isolated either as the protected silyl enol ethers **3** or as the corresponding free 4-oxo hydrazones **4** (Scheme 1). Release of the chiral auxiliary from the latter following the established deprotecting protocols was accomplished to synthesize a variety of enantiomerically enriched 1,4-dicarbonyl compounds including 4-oxo aldehydes, 4-oxo nitriles, and 4-oxo carboxylic acids.

On the other hand, the azomethine carbon of hydrazones can also behave as an electrophilic center of low reactivity (thereby acting as electron-rich imines), able to suffer addition of strong nucleophiles such as organometallic reagents.[10,11] Furthermore, the use of chiral hydrazones to achieve stereocontrol during the above reaction is a well-established method for the asymmetric

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(1) Brehme, R. *Chem. Ber.* **1990**, *123*, 2039. Brehme, R.; Nikolajewski, H. E. *Tetrahedron Lett.* **1982**, *23*, 1131. Brehme, R.; Nikolajewski, H. E. *Tetrahedron* **1976**, *32*, 731.

(2) Kamitori, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokohama, T. *J. Org. Chem.* **1988**, *53*, 129. Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T.; Ohara, S.; Yamada, K.; Yoshikawa, N. *J. Org. Chem.* **1988**, *53*, 519.

(3) (a) Lassaletta, J. M.; Fernández, R. *Tetrahedron Lett.* **1992**, *33*, 3691. (b) Lassaletta, J. M.; Fernández, R.; Gasch, C.; Vázquez, J. *Tetrahedron* **1996**, *52*, 9143. (c) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 627. (d) Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 48.

(4) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Pareja, C. *Tetrahedron Lett.* **1996**, *37*, 5787.

(5) (a) Lassaletta, J. M.; Fernandez, R.; Martín-Zamora, E.; Díez, E. *J. Am. Chem. Soc.* **1996**, *118*, 7002. (b) Díez, E.; Fernández, F.; Gash, C.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E.; Vázquez, J. *J. Org. Chem.* **1997**, *62*, 2, 5144.

(6) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Vázquez, J.; Díez, E.; Monge, A.; Lassaletta, J. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 349.

(7) Volkmann A. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 1, Chapter 1.12.

(8) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Vázquez, J. *Tetrahedron Lett.* **1993**, *34*, 141.

(9) (a) Preparation: Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 48. (b) For a review on the use of formaldehyde SAMP-hydrazone as chiral, neutral formylating reagent see: Enders, D.; Bolkenius, M.; Vázquez, J.; Lassaletta, J. M.; Fernández, R. *J. Prakt. Chem.* **1998**, *340*, 281.

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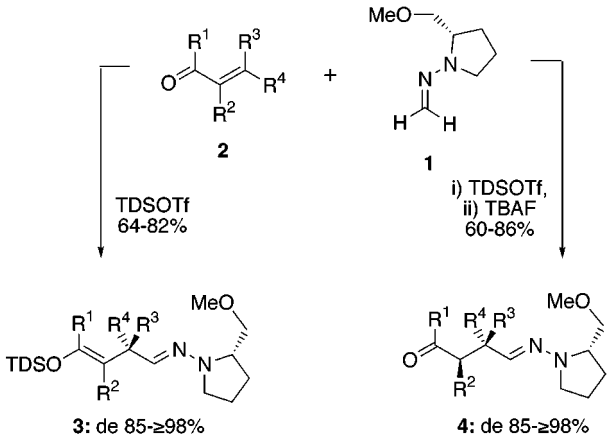
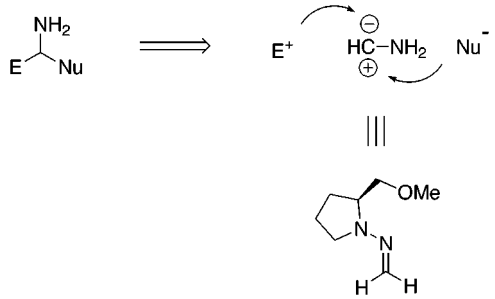
Scheme 1



Scheme 2

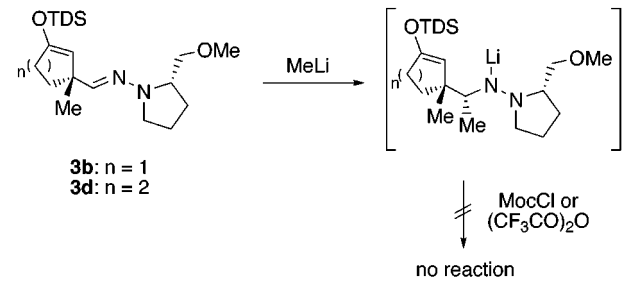


synthesis of optically enriched amines,[12] and in particular, SAMP derivatives have proved to be particularly well suited for this purpose.[13] In this context, we decided to take advantage of this reaction for the optimal employment of the chiral information in the original reagent: After the excellent induction effected in the addition of SAMP-hydrazone **1** as a d^1 synthon (Umpolung), the chiral auxiliary can be used again for the stereocontrolled generation of a second chiral center. Considering the whole process, an aminomethine fragment would then be inserted between the enone skeleton and the organic rest from the organometallic reagent. Thus, the original retrosynthetic analysis depicted in Scheme 2 can be formulated, thereby highlighting the versatility of the azomethine carbon atom of hydrazones being object of sequential electrophilic and nucleophilic attacks.

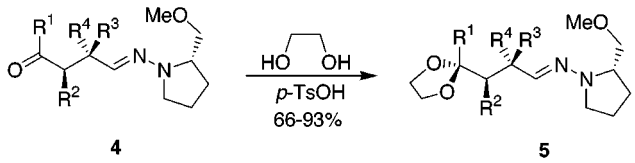
Results and Discussion

Considering the remarkable stability of the dimethylthexylsilyl (TDS) group, direct addition of MeLi was

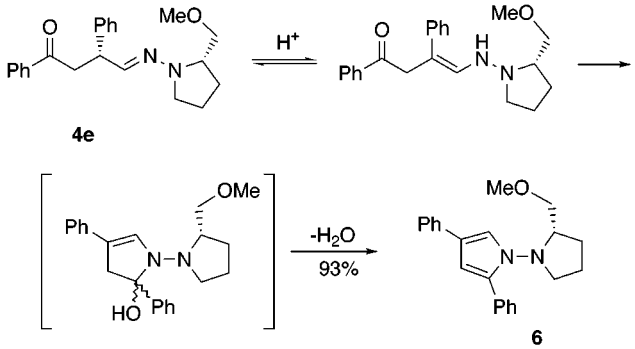
Scheme 3



Scheme 4



Scheme 5



first essayed using the more stable and nonenolizable quaternary compounds **3b,d** as substrates (Scheme 3). In fact, the addition reaction to hydrazones **3b,d** using MeLi as such or in situ transmetalated cerium reagent[14] led to complete consumption of the starting material. Unfortunately, the corresponding intermediate hydrazines proved to be rather unstable and did not survive chromatographic purification. Any attempt to trap their anions as methoxycarbonyl or trifluoroacetyl derivatives was unsuccessful, presumably because of the considerable steric hindrance around the extremely big TDS group. Therefore, compounds **4** were reacted with ethylene glycol in refluxing benzene in the presence of catalytic amounts of acid (*p*-TsOH) affording the corresponding ethylene ketals **5** in good yields (Scheme 4). As a particular case, chalcone-derived adduct **5e** could not be prepared under these conditions; 2,4-diphenyl-1-[2-(methoxymethyl)pyrrolidyl]pyrrole (**6**) was obtained instead in 93% yield (Scheme 5). This result may be explained assuming that an intramolecular cyclodehydration reaction takes place via enhydrazine tautomers. Although hydrazone−enhydrazine tautomerism is in general not a favored process, it is assisted in this case by conjugation with the phenyl group at C-2 and cyclization by attack of the hydrazine to the relatively unreactive aromatic carbonyl. On the other hand, attempts to obtain the corresponding ketone ethylene dithioketal under standard conditions [ethane-

(10) For a recent, comprehensive review on asymmetric addition of organometallics to the CN double bond of hydrazones see: Enders, D.; Reinhold, U. *Tetrahedron Asymmetry* **1997**, *8*, 1895.

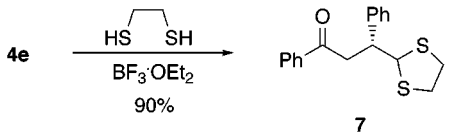
(11) Very recently, Kobayashi et al. have reported on the rare earth triflate-catalyzed addition of silyl enolates to monoacylhydrazones: (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1998**, 1019. The addition of these weaker nucleophiles, however, appears to be restricted to activated hydrazones.

(12) (a) Takahashi, H.; Tomita, K.; Otomasu, H. *J. Chem. Soc., Chem. Commun.* **1979**, 668. (b) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265. (c) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429. (d) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Manganey, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038. (e) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.*, **1996**, *37*, 5543. (f) Bataille, P.; Paterne, M.; Brown, E. *Tetrahedron Asymmetry* **1998**, *9*, 2181. (g) Hsieh, Y.-T.; Lee, G.-H.; Wang, Y.; Luh, T.-Y. *J. Org. Chem.* **1998**, *63*, 1484.

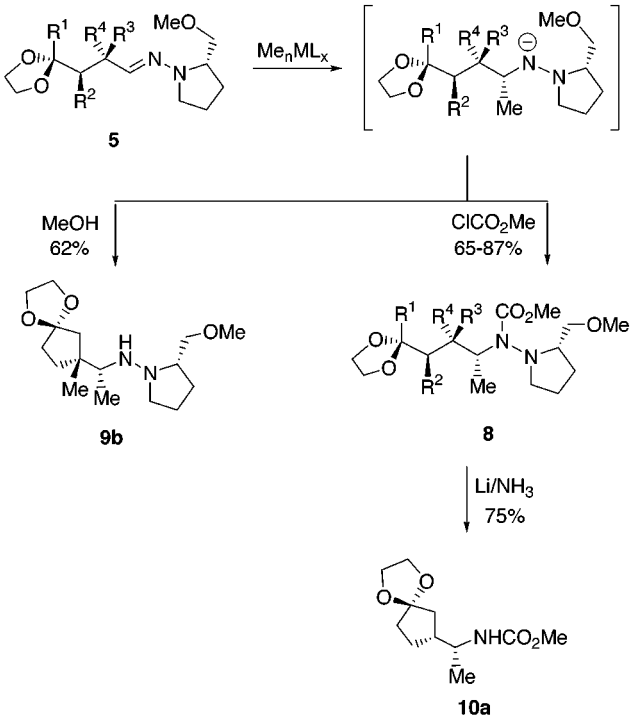
(13) (a) Enders, D.; Nübling, C.; Schubert, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109. (b) Enders, D.; Nübling, C.; Schubert, H. *Liebigs Ann.* **1997**, 1089 and references therein. (c) Denmark, S. E.; Weber, T.; Piotrowski D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224.

(14) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N.; *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (c) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *C21*, 285. (d) Imamoto, Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.

Scheme 6



Scheme 7



dithiol/CSA or $BF_3{\cdot}Et_2O$] also failed; the dithiolane derivative **7**, resulting from thiolysis of the hydrazone moiety, was obtained instead in almost quantitative yield (Scheme 6). This interesting result open new perspectives for dialkyl hydrazones, as the chemistry of dithioketals (desulfurization, carbanion chemistry, etc.) complement the range of functional group transformations (to aldehydes, nitriles, carboxylic acids) and carbon−carbon bond-forming reactions available for them.[15]

Quaternary compounds **5b,d** were then treated with excess of MeLi (4 equiv) and reacted (−78 °C → rt (room temperature)) until consumption of the starting material. The intermediate hydrazines were reacted with excess of methyl chloroformate (MocCl) to afford their *N*-protected Moc-derivatives **8b,d** (Scheme 7). Despite the limited stability against oxidation usually exhibited by this type of hydrazines, unprotected adduct **9b** survived chromatographic purification and could be isolated in 62% yield (Table 1, entry 6). Although a high diastereoselectivity for the addition of organometallic compounds to proline-derived chiral hydrazones has been regularly observed,[13] some uncertainty about the result was raised in this case as a consequence of the presence of the neighbor stereogenic center in position α to the C=N bond. Theoretically, the effect of this center can either cooperatively increase the asymmetric induction originated by C-2 in the pyrrolidine ring or act in a "mismatched" way to drop the good de values usually observed for these systems. The results collected in Table 1 (de 88% and 86% for **8b**,**d**, respectively), however, are similar to those reported for the addition of alkyllithium reagents to SAMP-derived hydrazones lacking such an adjacent stereogenic center, suggesting that control by chelation, as observed in related systems,[13b] is by far predominant over the steric influence of this center.[16]

The addition of MeLi to enolizable hydrazones **5a,c**, however, afforded more complicated mixtures indicating that some racemization (aza-enolization) occurs under the reaction conditions. To optimize conditions, a comparative study using cyclopentenone derivative **5a** as the model substrate and several reagents MeLi, MeLi/$CeCl_3$,[17] MeMgBr, and MeMgBr/$CeCl_3$ was performed. The analysis of the results summarized in Table 1 (entries 1−4) is rather surprising: As in the case of MeLi, organocerium reagents also produced some racemization, as deduced from the presence of at least three different diastereoisomers in the reaction mixtures. On the other hand, the addition of MeMgBr in toluene unexpectedly gave the best results, affording mixtures of only two diastereomers for **8a** (87%, dr 79:21) and **8c** (75%, dr 86:14). These results are only consistently assuming that the reaction proceeds without racemization at the center α to the hydrazone. The lower selectivity here observed with respect to that in the quaternary substrates indicates a higher mismatching effect, which can be explained considering that the steric difference between the "small" (hydrogen) and "medium" (methylene in the cyclopentane ring) substituents in these cases are clearly higher. The diastereomeric mixture obtained from **5a** could be completely separated by flash chromatography to afford optically pure (*S*,*R*,*R*)- and (*S*,*S*,*R*)-**8a** in 69% and 18% yield, respectively. The major isomer (*S*,*R*,*R*)-**8a** was then treated with lithium in liquid ammonia[18] to afford the corresponding Moc-protected amine **10a** in 75% yield (Scheme 7).

Additionally, a "one-pot" synthesis of γ-amino ketone derivatives could be also achieved from ketals **5a**−**d** by addition of the organometallic reagent followed by Raney nickel-catalyzed hydrogenolysis.[19] Thus, the crude mixture containing the unstable hydrazines was redissolved in methanol and stirred in the presence of the catalyst under an hydrogen atmosphere until TLC indicated total consumption of the hydrazine. After removal of the catalyst by filtration, the desired amines were protected in situ by adding Boc_2O/Et_3N to the resulting methanolic solution, and their corresponding *N*-Boc derivatives **11a**−**d** (Scheme 8) could be isolated in satisfactory yields (53−65% overall from **5**) and with diastereoselectivities very similar to those observed for the corresponding *N*-Moc-hydrazines **8a**−**d**. The results for the synthesis of compounds **11** are summarized in Table 2.

(15) The scope and limitations of the direct thioketalation of hydrazones has been investigated: Díez, E.; López, A. M.; Pareja, C.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M. *Tetrahedron Lett.* **1998**, *39*, 7955.

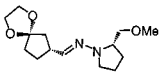
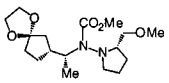
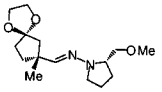
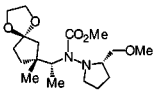
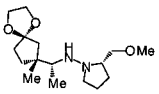
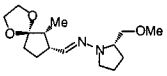
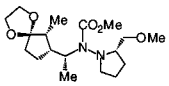
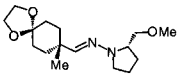
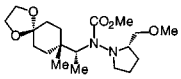
(16) It should be noted that the steric differences between the "small" (methyl) and "medium" (methylene in the ring) substituents in these cases are clearly less than for the tertiary compound.

(17) Organocerium compounds are claimed to possess better nucleophilicity and less basic character than organolithium or Grignard reagents: Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 8, 569 and references therein.

(18) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 5, 6219.

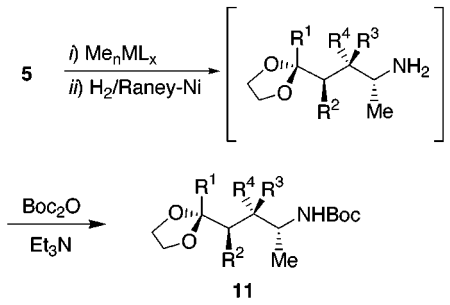
(19) It is important to wash the catalyst repeatedly with water to neutrality and then with methanol prior to use. Direct washing of the catalyst with methanol resulted in the unexpected N-methylation of the resulting amines. For instance, up to 39% of the *N*,*N*-dimethylamine derivative shown in Figure 1 was obtained from **5b** under these conditions.

Table 1. Synthesis of Hydrazines 8a–d and 9b

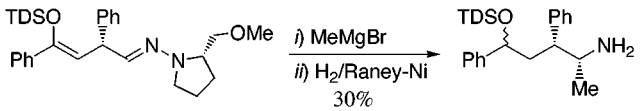
entry	starting material	reagent	solvent	major product	yield (%)	dr[a]
1	 **5a**	MeLi	THF	 **8a**	80	62:24:14
2		$MeLi/CeCl_3$	THF		81	62:23:15
3		MeMgBr	toluene		87	79:21[b]
4		$MeMgBr/CeCl_3$	THF		79	70:30
5	 **5b**	MeLi	THF	 **8b**	65	94:6
6	**5b**	MeLi	THF	 **9b**	62[c]	93:7
7	 **5c**	MeMgBr	toluene	 **8c**	75	86:14
8	 **5d**	MeLi	THF	 **8d**	65	93:7

[a] Determined by ^{13}C and ^{1}H NMR spectroscopy. [b] This mixture was separated by flash chromatography. [c] Unstable compound.

Scheme 8



Scheme 9



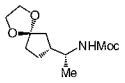
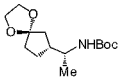
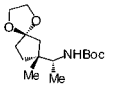
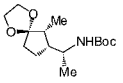
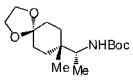
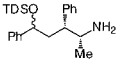
3e **12**

Finally, the unsuccessful attempts described above for the preparation of the ethylene ketal from **4e** prompted us to essay the direct addition of MeMgBr to **3e** followed by in situ hydrogenolysis (Raney nickel) of the obtained reaction mixture (Scheme 9). This experiment took place with limited success: the expected dimethylthexylsilyl ether **12**, in which the enolic double bond has been obviously reduced, was isolated as a mixture of only two diastereomers in 88:12 ratio. Although this indicates that the hydrogenation of the enolic double bond takes place in a highly stereoselective way, the overall yield was quite low (30%).

Stereochemical Aspects

The stereochemistry of the addition is assumed to be controlled by chelation of the organometallic reagent by the oxygen in the methoxymethyl group and the hydrazone π-system as previously proposed.[13] According to this model, the *R* configuration is assigned to the new stereogenic center generated in the addition of the organometallic reagent to SAMP-hydrazones. In addition, the configuration of the newly created stereogenic center

Table 2. Synthesis of Amino Ketone Derivatives 10–12

entry	starting material	product	reagent/ solvent (addition step)	yield (%)	isomers ratio[a]
1	(*S*,*R*,*R*)-**8a**	 **10a**	$Li/NH_3/THF$	75	-[b]
2	**5a**	 **11a**	MeMgBr/toluene	60	74:26
3	**5b**	 **11b**	MeLi/THF	65	93:7
4			MeMgBr/toluene	60	91:9
5	**5c**	 **11c**	MeMgBr/toluene	53	88:12
6	**5d**	 **11d**	MeLi/THF	57	91:9
7	**3e**	 **12**	MeMgBr/THF	30	88:12

[a] Determined by ^{1}H and ^{13}C NMR spectroscopy of the crude mixtures. [b] de ≥98%.

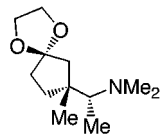


Figure 1.

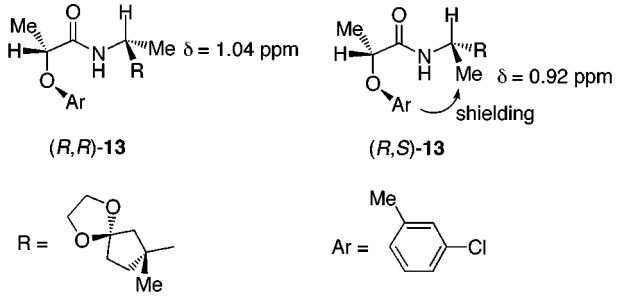


Figure 2.

of compound **8b** was established following the methodology recently developed by Nájera et al.[20] Thus, the crude diastereomeric mixture obtained from **5b** after addition of MeLi and Raney nickel-catalyzed hydrogenolysis was reacted with (*R*)-*O*-(4-chloro-2-methylphenyl)lactyl chloride to obtain the corresponding amide **13** as a 93:7 mixture of diastereoisomers (Figure 2). The ^{1}H NMR spectrum recorded for this compounds showed the presence of two doublets at 1.04 and 0.92 ppm assigned to the methyl groups at the new stereogenic center of the major and minor isomers, respectively. These data are in excellent agreement with those observed for closely related structures,[20] and according to the method, the signal at δ 1.04 ppm (major isomer) can be assigned to the (*R*,*R*)-configurated product, while that at δ 0.92 ppm (minor isomer), clearly shielded by the aromatic rest, should correspond to the (*R*,*S*)-epimer.

To further support the model previously proposed[13b] to explain the stereochemical results, ab initio MO calculations for the reaction of MeLi with acetaldehyde SAMP-hydrazone have been carried out. These compounds can be considered as models of the experimentally studied ones whereas maintaining the computational cost at an acceptable level. All the calculations were performed using Gaussian98[21] with the standard 6-31G** basis set[22] and the Hartree−Fock (HF) and B3-LYP[23] methods. All the structures were fully characterized by harmonic analysis. Both levels gave chemically equivalent results; from now on we will discuss on the basis of the B3-LYP data. As the formation of organometallic reagent/SAMP-hydrazone complexes is assumed to occur previous to the addition, we started by searching the possible structures for these complexes. Two different geometries **A** and **B** [essentially six- and five-membered complexes by coordination of the lithium atom with N(2) and N(1), respectively] for the MeLi-complexed acetaldehyde SAMP-hydrazone were found at close energetic levels (Figure 3, Table 3). The analysis of the structural features of **A** and **B** reveals the dihedral angle C(5)−N(1)−N(2)−C(1′) (−35.8 and −85.8°, respectively) as one of the most significant geometric differences. The higher deviation of planarity observed in structure **B** is attributed to the loss of conjugation between the amino nitrogen N(1) (lone pair) and the CN double bond as a consequence of the coordination of the former with the lithium atom. As the electrophilic character of the azomethine carbon is associated with nonplanar conformations,[24] it was anticipated that complex **B** should have a stronger affinity for nucleophilic species. In fact, the calculated CHELPG[25] charges on C(1′) for complexes **A** and **B** are +0.06 and +0.44, respectively (Table 3). This strong difference suggests that the latter should be the reactive species. A transition state (**TS**) connecting **B** with the adduct **P** have been localized. Moreover, the comparison between **B** and **TS** reveals close geometries (Figure 3), the main differences being the shorter C(1′)−C(1″) distance (3.82 Å in **B**; 2.32 Å in **TS**) and the lower electronic density on C(1″) (−0.84 in **B**; −0.60 in **TS**) (Table 3). The low energy barrier required to reach the TS (6.75 kcal mol^{-1}) is consistent with the mild experimental conditions and results in the transfer of the methyl group to the *Re* face of the CN double bond, according with the experimental observations. Although the presumably important solvent effects have not been included in these studies, the uniformity of the stereochemical results observed in a variety of solvents, including a noncoordinating one (toluene), supports the qualitative validity of the study.

In summation, formaldehyde SAMP-hydrazone behaves as an ambiphilic chiral aminomethine synthon, their azomethine carbon being able to suffer both the electrophilic attack of conjugated enones and the nucleophilic addition of organometallic reagents. This synthetic strategy is illustrated in the asymmetric synthesis of γ-amino ketone derivatives containing up to three newly created stereogenic centers. As a singular limitation, the method appear to be inappropriate for chalcone-derived substrates, due to the unavailability of suitable ketalized derivatives.

Experimental Section

General Experimental Data. Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or $CDCl_3$ (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference or C_6D_6 or DMSO-d_6 using the solvent

(20) Chinchilla, R.; Falvello, L. R.; Nájera, C. *J. Org. Chem.* **1996**, *61*, 1, 7285.

(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria G. E.; Robb M. A.; Cheeseman J. R.; Zakrzewski V. G.; Montgomery J. A.; Stratmann R. E.; Burant J. C.; Dapprich S.; Millam J. M.; Daniels A. D.; Kudin K. N.; Strain M. C.; Farkas O.; Tomasi J.; Barone V.; Cossi M.; Cammi R.; Mennucci B.; Pomelli C.; Adamo C.; Clifford S.; Ochterski J.; Petersson G. A.; Ayala P. Y.; Cui Q.; Morokuma K.; Malick D. K.; Rabuck A. D.; Raghavachari K.; Foresman J. B.; Cioslowski J.; Ortiz J. V.; Stefanov B. B.; Liu G.; Liashenko A.; Piskorz P.; Komaromi I.; Gomperts R.; Martin R. L.; Fox D. J.; Keith T.; Al-Laham M. A.; Peng C. Y.; Nanayakkara A.; Gonzalez C.; Challacombe M.; Gill P. M. W.; Johnson B. G.; Chen W.; Wong M. W.; Andres J. L.; Head-Gordon M.; Replogle E. S.; Pople J. A. *Gaussian 98W (Revision A.3)*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(22) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.

(23) (a) Becke, A. D. *J. Chem. Phys.* **1993,** *98*, 5648. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (c) Lee, C.; Yang, W. Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(24) In full analogy with enamines, the nucleophilic character of the azomethine carbon of hydrazones demands an effective conjugation between the amino nitrogen and the CN double bond. Consequently, the electrophilic, imine-like reactivity of hydrazones requires the loss of conjugation and, hence, conformations clearly deviated from planarity. Pappalardo, R. R.; Muñoz, J. M.; Fernández, R.; Lassaletta, J. M., Unpublished results.

(25) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

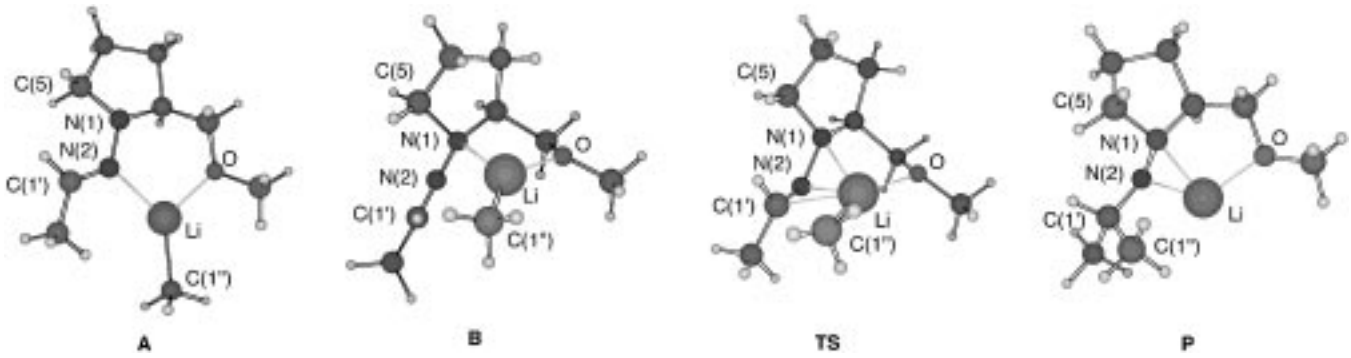


Figure 3.

Table 3. Relative Energies (kcal/mol) and Selected CHELPG Charges Calculated for the Complexes A and B, Transition State TS, and Adduct P

	HF/6−31G**					B3-LYP/6-31G**				
	E	$q_{C(1')}$	$q_{C(1'')}$	$q_{N(1)}$	$q_{N(2)}$	ΔE	$q_{C(1')}$	$q_{C(1'')}$	$q_{N(1)}$	$q_{N(2)}$
A	+0.99	+0.15	−0.86	−0.44	−0.16	-3.80	+0.06	−0.81	−0.32	−0.08
B	0.00	+0.51	−0.88	−0.16	−0.67	0.00	+0.44	−0.85	+0.18	−0.58
TS	20.59	+0.50	−0.64	−0.51	−0.63	6.75	+0.39	−0.60	−0.47	−0.50
P	−23.82	+0.74	−0.38	−0.59	−0.98	−31.6	+0.65	−0.31	−0.56	−0.87

as an internal reference. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were obtained at 70 eV, using an ionizing current of 100 μA, an accelerating voltage of 4 KV, and a resolution of 1000 or 10 000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by flash chromatography (silica gel). The light petroleum ether (PE) used had boiling range 40−65 °C. Tetrahydrofuran (THF), benzene, and toluene were distilled from sodium−benzophenone ketyl immediately prior to use. Compounds **3** and **4** were synthesized as described earlier.[5]

Synthesis of Moc-Hydrazines 8. Method A. Dry THF (19 mL) was cooled at −78 °C in a round-bottom flask under an argon atmosphere. MeLi (1.6 M in Et_2O, 3.75 mL, 6 mmol) was added, the mixture was stirred for 5 min, and then a solution of hydrazone **5** (1 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and then at room temperature until total consumption of the starting material (TLC monitoring). Methyl chloroformate (MocCl, 0.930 mL, 12 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was poured on water and extracted with Et_2O. The ethereal phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was purified by flash chromatography.

Method B. $CeCl_3$ (498 mg, 2 mmol) was dried (140 °C, 0.06 mmHg) for 2 h in a two-necked round-bottom flask. The flask was then cooled to room temperature, and dry THF (40 mL) was added under an argon atmosphere. The resulting mixture was stirred for 2 h at room temperature and then cooled to −78 °C. MeLi (1.6 M in Et_2O, 3.75 mL, 6 mmol) was added, and the mixture was stirred for 1 h at −78 °C and then at room temperature until homogeneity (5 min) and then cooled again to −78 °C. A solution of the hydrazone **5** (1 mmol) in dry THF (3 mL) was added dropwise, and the mixture was stirred for 1 h at −78 °C and then at room temperature until total consumption of the starting material (TLC monitoring). MocCl (0.93 mL, 12 mmol) was added, and the mixture was stirred for 24 h at room temperature and then poured on H_2O and extracted with Et_2O. The ethereal phase was treated as described above for method A.

Method C. To a stirred, cooled (−78 °C) solution of the hydrazone **5** (1 mmol) in dry toluene (40 mL) was added MeMgBr (3 M in Et_2O, 1.7 mL, 5 mmol) under an argon atmosphere. The mixture was then allowed to warm to 0 °C and stirred until total consumption of the starting material. MocCl (0.93 mL, 12 mmol) was added, and the mixture was stirred for 24 h at room temperature and processed as described above for method A.

Method D. This followed the procedure described for method B but used MeMgBr (3 M in Et_2O, 1.7 mL, 5 mmol) instead of MeLi.

The methods followed for synthesis, chromatography solvents, yields, and spectral and analytical data for compounds **8** are as follows:

8a. Following method C from **5a**, flash chromatography (1:1 Et_2O−PE) afforded (*S*,*R*,*R*)-**8a** (236 mg, 69%) as an oil: $[\alpha]^{rt}_D$ −60.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 1.07 (d, 3H, J = 6.7 Hz), 1.29−1.38 (m, 1H), 1.39 (ddd, 1H, J = 0.8, 9.9, 13.2 Hz), 1.49−1.55 (m, 1H), 1.60−1.69 (m, 3H), 1.75−1.82 (m, 2H), 1.84 (dd, 1H, J = 7.8, 13.2 Hz), 1.98 (dq, 1H, J = 8.2, 11.6 Hz), 2.17−2.22 (m, 1H), 2.95−3.00 (m, 1H), 3.02 (dt, 1H, J = 3.5, 8.0 Hz), 3.12 (dd, 1H, J = 7.8, 9.6 Hz), 3.24 (s, 3H), 3.26 (dd, 1H, J = 4.1, 9.6 Hz), 3.31−3.36 (m, 1H), 3.59 (s, 3H), 3.63−3.71 (m, 1H), 3.74−3.83 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 17.3, 23.0, 27.5, 27.6, 35.1, 40.0, 41.2, 51.7, 53.9, 58.2, 59.9, 61.9, 63.4, 63.6, 75.2, 116.8, 154.9; IR (film, cm^{-1}) 1699; mass spectrum *m*/*z* (rel intensity) 342 M^+ (2), 297 (100). Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.63; H, 8.83; N, 8.18. Found: C, 59.38; H, 9.01; N, 8.07.

Eluted also (*S*,*S*,*R*)-**8a** (62 mg, 18%) as an oil: $[\alpha]^{rt}_D$ −53.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 1.10 (d, 3H, J = 6.7 Hz), 1.20−1.30 (m, 1H), 1.48 (dd, 1H, J = 10.3, 13.2 Hz), 1.55 (dq, 1H, J = 3.8, 15.9 Hz), 1.60−1.88 (m, 6H), 1.95−2.06 (m, 1H), 2.17−2.30 (m, 1H), 2.99−3.15 (m, 3H), 3.23 (s, 3H), 3.33−3.40 (m, 2H), 3.61 (s, 3H), 3.65−3.75 (m, 1H), 3.75−3.83 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 16.4, 22.6, 26.9, 27.1, 35.2, 40.1, 41.0, 51.3, 53.6, 57.7, 59.1, 61.8, 63.1, 63.3, 74.8, 116.2, 154.9.

8b. Following method A from **5b**, flash chromatography (2:5 Et_2O−PE) afforded (*S*,*R*,*R*)-**8b** (232 mg, 65%) as an oil: $[\alpha]^{rt}_D$ −39.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 1.06 (s, 3H), 1.19 (d, 3H, J = 7.0 Hz), 1.32−1.70 (m, 7H), 1.50 (d, 1H, J = 14.2 Hz), 1.90 (d, 1H, J = 14.2 Hz), 1.93−2.05 (m, 1H), 2.95−3.05 (m, 1H), 3.12−3.17 (m, 1H), 3.17 (dd, 1H, J = 7.5, 9.4 Hz), 3.23 (s, 3H), 3.30−3.40 (m, 1H), 3.36 (dd, 1H, J = 4.4, 9.4 Hz), 3.42−3.51 (m, 1H), 3.60 (s, 3H), 3.71−3.81 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 13.9, 22.9, 23.9, 27.5, 34.4, 35.0, 44.1, 46.7, 51.5, 53.9, 57.9, 62.7, 63.1, 63.3, 64.8, 75.2, 117.1, 155.5; IR (film, cm^{-1}) 1701; mass spectrum *m*/*z* (rel intensity) 356 M^+ (3), 143 (100). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.45; H, 8.86; N, 7.65.

8c. Following method C from **5c**, flash chromatography (1:2 Et_2O−PE) afforded (*S*,*R*,*R*,*R*)-**8c** (267 mg, 75%) as an oil: $[\alpha]^{rt}_D$ −69.6 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 0.93 (d, 3H, J = 6.7 Hz), 1.16 (d, 3H, J = 7.0 Hz), 1.32−1.42

(m, 1H), 1.50−1.58 (m, 1H), 1.60−1.71 (m, 5H), 1.74−1.84 (m, 2H), 1.94−2.05 (m, 1H), 3.00−3.10 (m, 2H), 3.14 (dd, 1H, J = 7.7, 9.5 Hz), 3.24 (s, 3H), 3.29 (dd, 1H, J = 4.1, 9.5 Hz), 3.34−3.40 (m, 1H), 3.61 (s, 3H), 3.73−3.86 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 15.3, 17.3, 22.9, 25.2, 27.3, 33.2, 43.0, 47.6, 51.6, 53.9, 58.0, 59.7, 62.1, 63.4, 63.9, 74.9, 117.3, 155.2; IR (film, cm^{-1}) 1699; mass spectrum *m/z* (rel intensity) 356 M$^+$ (6), 311 (100). Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.73; H, 9.05; N, 7.86. Found: C, 60.90; H, 9.09; N, 7.77.

8d. Following method A from **5d**, flash chromatography (1:2 Et_2O−PE) afforded (*S*,*R*,*R*)-**8d** (241 mg, 65%) as an oil: $[\alpha]^{rt}_D$ −59.0 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 1.00 (s, 3H), 1.19 (d, 3H, J = 7.1 Hz), 1.22−1.70 (m, 9H), 1.46 (d, 1H, J = 7.9 Hz), 1.75−1.85 (m, 1H), 1.95−2.05 (m, 1H), 2.90−3.05 (m, 1H), 3.10−3.18 (m, 1H), 3.18−3.21 (m, 1H), 3.23 (s, 3H), 3.30−3.50 (m, 2H), 3.59 (s, 3H), 3.77−3.87 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 13.3, 18.8, 21.5, 23.0, 27.5, 33.5, 34.2, 39.7, 42.8, 51.4, 54.0, 57.9, 62.8br, 62.9, 63.5, 65.5br, 75.3, 108.4, 155.7; IR (film, cm^{-1}) 1748, 1701; mass spectrum *m/z* (rel intensity) 370 M$^+$ (3), 325 (100). Anal. Calcd for $C_{19}H_{34}N_2O_5$: C, 61.59; H, 9.25; N, 7.56. Found: C, 61.42; H, 9.18; N, 7.73.

Synthesis of Hydrazine 9b. Dry THF (19 mL) was cooled at −78 °C in a round-bottom flask under an argon atmosphere. MeLi (1.6 M in Et_2O, 3.75 mL, 6 mmol) was added, the mixture was stirred for 5 min, and then a solution of hydrazone **5b** (1 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature. After TLC indicated total consumption of the starting material, methanol (5 mL) was added and the mixture was stirred 10−15 min. The mixture reaction was poured on water and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting residue was purified by flash chromatography (1:2 Et_2O−PE) affording (*S*,*R*,*R*)-**9b** (185 mg, 62%) as an oil: $[\alpha]^{rt}_D$ −110.3 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.2 Hz), 1.01 (s, 3H), 1.64 (d, 1H, J = 4.1 Hz), 1.50−2.20 (m, 10H), 1.80 (d, 1H, J = 4.1 Hz), 2.49−2.53 (m, 1H), 2.68 (q, 1H, J = 6.2 Hz), 3.34 (dd, 1H, J = 6.7, 9.0 Hz), 3.36 (s, 3H), 3.42−3.46 (m, 1H), 3.58 (dd, 1H, J = 3.6, 9.0 Hz), 3.85−3.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 20.8, 21.5, 26.2, 35.0, 35.5, 43.2, 48.1, 56.4, 59.0, 62.2, 63.8, 64.2, 65.4, 75.0, 117.7; IR (film, cm^{-1}) 2880, 1454; mass spectrum *m/z* (rel intensity) 298 M$^+$ (15), 157 (100); *m/z* calcd for $C_{16}H_{30}N_2O_3$ 298.2256, found 298.2255.

Synthesis of 10a. A solution of (*S*,*R*,*R*)-**8a** (1 mmol) in dry THF (1 mL) was mixed with ammonia (15 mL) at −78 °C, and the mixture was treated with clean Li wire (8 mmol). The resulting blue solution was allowed to stir for 1.5 h at −33 °C, NH_4Cl (12 mmol) was added, and the ammonia allowed to evaporate. The residue was dissolved in H_2O (40 mL) and extracted with Et_2O. The organic phase was dried (Na_2SO_4) and concentrated, and the resulting residue was purified by flash chromatography (1:1 Et_2O−PE + 1% Et_3N) affording 171.7 mg (75%) of crystalline **10a**: mp 42−44 °C; $[\alpha]^{rt}_D$ −0.7 (*c* 1, MeOH); ^{1}H NMR (500 MHz, C_6D_6, 40 °C) δ 0.86 (d, 3H, J = 6.6 Hz), 1.32 (dq, 1H, J = 9.1, 12.6 Hz), 1.49 (dd, 1H, J = 8.7, 12.4 Hz), 1.53−1.59 (m, 1H), 1.66−1.86 (m, 3H), 1.81 (dd, 1H, J = 8.2, 12.6 Hz), 3.43−3.51 (m, 4H), 3.47 (s, 3H), 3.63 (br s, 1H), 4.23 (br s, 1H); ^{13}C NMR (125 MHz, C_6D_6, 40 °C) δ 19.8, 26.5, 36.1, 39.9, 43.6, 50.9, 51.5, 64.3, 64.3, 117.7, 156.5; IR (film, cm^{-1}) 3335, 1721; mass spectrum *m/z* (rel intensity) 229 M$^+$ (1), 127 (100); *m/z* calcd for $C_{11}H_{19}NO_4$ 229.1314, found 229.1312.

Synthesis of Boc-Amines 11. Method A. Dry THF (19 mL) was cooled at −78 °C in a round-bottom flask under an argon atmosphere. MeLi (1.6 M in Et_2O, 3.75 mL, 6 mmol) was added, the mixture was stirred for 5 min, and then a solution of hydrazone **5** (1 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred for 1 h at −78 °C and then at room temperature until TLC indicated total consumption of the starting material. MeOH (5 mL) was added, and the mixture was poured on water and extracted with Et_2O. The combined ethereal phase was dried (Na_2SO_4) and concentrated, and the resulting residue was solved in MeOH (25 mL). Raney nickel (50% in H_2O, 0.8 g, washed with H_2O and MeOH) was added, and the mixture was stirred under H_2 (700 psi, 50 °C) until consumption of the starting material (TLC, ca. 24 h). The mixture was then filtered through Celite and treated with a di-*tert*-butyl dicarbonate (Boc_2O, 327 mg, 1.5 mmol) solution in MeOH (3 mL) and Et_3N (7.5 mL). The mixture was stirred for 8−10 h (TLC monitoring), concentrated, solved in CH_2Cl_2, washed with brine and H_2O, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography.

Method B. To a stirred, cooled (−78 °C) solution of the hydrazone **5** (1 mmol) in dry toluene (40 mL) was added MeMgBr (3 M in Et_2O, 1.7 mL, 5 mmol) under an argon atmosphere. The mixture was then allowed to warm to 0 °C and stirred until total consumption of the starting material (TLC). The mixture was then washed with saturated NH_4Cl solution, the aqueous layer washed with Et_2O, and the combined organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was then treated as described for method A.

The methods followed for synthesis, chromatography solvents, yields, and spectral and analytical data for compounds **11** are as follows:

11a. Following method B from **5a**, flash chromatography (1:2 Et_2O−PE + 1% Et_3N) afforded **11a** (163 mg, 60%) as an oil: $[\alpha]^{rt}_D$ +3.6 (*c* 1.1, MeOH); ^{1}H NMR (500 MHz, C_6D_6, 40 °C) δ 0.85 (d, 3H, J = 6.6 Hz), 1.36 (dq, 1H, J = 9.2, 12.5 Hz), 1.45 (s, 9H), 1.51 (dd, 1H, J = 9.5, 12.8 Hz), 1.56−1.61 (m, 1H), 1.68−1.88 (m, 4H), 3.43−3.57 (m, 5H), 4.32−4.41 (br d, 1H); ^{13}C NMR (125 MHz, C_6D_6, 40 °C) δ 19.8, 26.1, 28.3, 35.5, 39.5, 43.6, 49.8, 64.0, 64.2, 78.8, 117.4, 155.5; IR (film, cm^{-1}) 1692; mass spectrum *m/z* (rel intensity) 271 M$^+$ (1), 127 (100); *m/z* calcd for $C_{14}H_{25}NO_4$ 271.1783, found 271.1782.

11b. Following method A from **5b**, flash chromatography (1:6 Et_2O−PE + 1% Et_3N) afforded **11b** (185 mg, 65%) as an oil: $[\alpha]^{rt}_D$ −2.8 (*c* 1, MeOH); ^{1}H NMR (300 MHz, distilled $CDCl_3$) δ 1.02 (s, 3H), 1.06 (d, 3H, J = 6.7 Hz), 1.36−1.95 (m, 4H), 1.44 (s, 9H), 1.59 (d, 1H, J = 13.9 Hz), 1.83 (d, 1H, J = 13.9 Hz), 3.50−3.70 (m, 1H), 3.86−3.91 (m, 4H), 4.65 (br s, 1H); ^{13}C NMR (125 MHz, distilled $CDCl_3$) δ 16.7, 22.6, 28.3, 33.6, 35.1, 44.0, 46.7, 53.5, 63.7, 64.2, 78.8, 117.6, 155.7; IR (film, cm^{-1}) 3350−3125, 2971, 1696; mass spectrum *m/z* (rel intensity) 285 M$^+$ (1), 212 (18), 168 (6), 144 (85), 141 (100), 127 (15), 99 (30). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.18; H, 9.02; N, 5.45.

11c. Following method B from **5c**, flash chromatography (1:4 Et_2O−PE + 1% Et_3N) afforded 151 mg (53%) of crystalline **11c**: mp 80−82 °C; $[\alpha]^{rt}_D$ −24.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6, 40 °C) δ 0.87 (d, 3H, J = 6.7 Hz), 1.07 (d, 3H, J = 6.8 Hz), 1.10−1.15 (m, 1H), 1.42−1.53 (m, 2H), 1.45 (s, 9H), 1.63−1.68 (m, 2H), 1.86−1.89 (m, 1H), 3.44−3.53 (m, 4H), 3.93 (br s, 1H), 4.22 (br d, 1H, J = 7.9 Hz); ^{13}C NMR (125 MHz, C_6D_6, 40 °C) δ 13.6, 19.8, 22.6, 28.6, 34.9, 43.3, 47.6, 50.1, 64.6, 64.8, 78.4, 118.2, 155.7; IR (film, cm^{-1}) 3380, 1688; mass spectrum *m/z* (rel intensity) 285 M$^+$ (3), 141 (100); *m/z* calcd for $C_{15}H_{27}NO_4$ 285.1940, found 285.1941.

11d. Following method A from **5d**, flash chromatography (1:4 Et_2O−PE + 1% Et_3N) afforded **11d** (170 mg, 57%) as an oil: $[\alpha]^{rt}_D$ −15.7 (*c* 1, MeOH); ^{1}H NMR (500 MHz, C_6D_6, 40 °C) δ 0.77 (s, 3H), 0.84 (d, 3H, J = 6.7 Hz), 1.10−1.31 (m, 2H), 1.38 (dt, 1H, J = 1.5, 13.7 Hz), 1.44 (s, 9H), 1.51 (d, 1H, J = 13.7 Hz), 1.51−1.59 (m, 3H), 1.63−1.67 (m, 1H), 3.44−3.53 (m, 4H), 3.91 (br s, 1H), 4.20 (br s, 1H); ^{13}C NMR (125 MHz, C_6D_6, 40 °C) δ 15.9, 19.8, 20.0, 28.6, 34.2, 35.3, 39.0, 43.4, 53.4, 64.0, 64.3, 109.6, 155.6; IR (film, cm^{-1}) 3352, 1694; mass spectrum *m/z* (rel intensity) 299 M$^+$ (1), 99 (100); *m/z* calcd for $C_{16}H_{29}NO_4$ 299.2096, found 299.2107.

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Supporting Information Available: The experimental procedures and spectral and analytical data for compounds **5a**−**d**, **6**, **7**, **12,** and **13** and the ^{13}C NMR spectra for compounds **5b,** (*S*,*S*,*R*)-**8a**, **9b**, **10a**, **11a**,**c**,**d**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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